REMARKS/ARGUMENTS

The Pending Claims

Before entry of the preceding Amendments, Claims 109-111 and 114-115 are pending in the above-captioned application. Claim 109 is directed to isolated 3'-phosphoadenosine-5' phosphosulfate (PAPS) synthetase protein. Claims 110-111 and 114-115 relate to human PAPS synthetase fusion protein.

Applicants' Amendment

Applicants have amended herein Claims 109-111 as further described below. No new matter is added by the amendments.

Claims 114-115 have been amended to change "TAT" to "Tat", which is merely intended as a refinement for greater clarity, in view of accepted usage, *e.g.*, Fawell *et al.* [PNAS USA, 91:664-668 (1994)]. No change in claim scope is intended by these amendments, nor is any new matter added thereby.

The Office Action and Applicants' Response

The Examiner acknowledged Applicants' Response to the restriction requirement in which Group I was elected without traverse. The Examiner also acknowledged the filing of the Amendment which Applicants mailed on May 20, 3003. The Examiner noted the cancellation of non-elected claims.

The Examiner required correction of the drawings. Accordingly, Applicants submit herein with replacement sheets (see page 4).

The Examiner objected to Claims 109-111 because the claims allegedly recite SEQ ID NO: with dashes and dots. In the Amendment filed on May 20, 2003, the SEQ ID NO: was corrected by strikethrough under the old rule 37 C.F.R. § 1.121, which made the claims appear to contain dots and dashes. Applicants apologize if this was unclear. The listing of the claims on page 2 clearly shows the amendments that have been made previously.

No claims were allowed. The following grounds of rejections were cited.

A. Rejections under 35 U.S.C. § 112

(1) The Examiner rejected Claims 110-111 and 114-115, under **35 U.S.C. §112, first paragraph**. The Examiner stated the following reasons:

Claims 110-111 & 114-115 are directed to an isolated PAPSS2 fusion protein (or PAPS synthetase which is known to have bi-functional ATP-sulfurylase and APS-kinase activities; or the sulfate activating enzymes) comprising a polypeptide having an amino acid sequence of SEQ ID NO:7, or 'gene-specific antibody binding fragment thereof at least 6 amino acids long' is meant to be. While antibodies are made against a protein, no binding fragment of the antibody against the gene or DNA or SEQ ID NO:9 is described. No specific examples are presented to describe such a construct. The prior art is silent about such or similar constructs that a skilled artisan could use in order to practice such an invention. The specification does not describe in clear terms even a single or representative number of species to the genus of fusion proteins using 6 amino acid fragments of SEQ ID NO:7. A 'representative number of species' requires that the species which are expressly described be representative of the entire genus. Therefore, without a clear description of even a single functional fusion peptide construct having the ATP-sulfurylase and APS kinase activities or that encoded by the nucleic acid of SEQ ID NO:9, adequate written description of the genus is not achieved by disclosing a vague genus. Therefore, the written description requirement is not satisfied.

Applicants have amended Claim 110 to delete the recitation of "or a gene-specific antibody-binding fragment thereof at least 6 amino acids long". Applicants also have amended Claim 111 to delete the recitations of "or a gene-specific fragment thereof" and "of either of these". In view of the amendment to Claims 110 and 111, Applicants believe the rejection of Claims 110-111 and 114-115 is overcome. Therefore, Applicants respectfully request the Examiner to withdraw the rejection of Claims 110-111 and 114-115 on this ground.

(2) Claims 110-111 and 114-115 were rejected under **35 U.S.C. §112, second paragraph**. Claim 110 and Claims 110 and 114-115 dependent therefrom were rejected for the reiterations of the expression "gene-specific antibody binding fragment".

Applicants have herein amended Claim 110 by deleting the term "gene-specific", which it is believed overcomes the rejection. In view of the amendment, Applicants respectfully request the Examiner to withdraw the rejection on this ground.

(3) Claims 109-111 and 114-115 were also rejected under **35 U.S.C. §112, second paragraph**. The Examiner asserted that Claims 109-110 recite uncommon abbreviations "PAPS" and "PAPSS2". Further, the Examiner found Claim 111 confusing because of the recitation "thereof" after the phrase referencing to a "nucleotide sequence".

Applicants have herein amended Claims 109 and 110 to indicate the full names: "3-phosphoadenosine-5' phosphosulfate" for "PAPS" and "human 3'-phosphoadenosine-5'-

phosphosulfate syntehtase" for "PAPSS2". Applicants also have amended Claim 111 by deleting the recitation of "or gene-specific fragment thereof" to overcome the rejection based on the term "thereof" in Claim 111.

In view of the amendments, Applicants respectfully request the Examiner to withdraw the rejection on this ground.

B. Rejections under 35 U.S.C. § 102

(1) The Examiner rejected Claim 109 under **35 U.S.C. §102(a)** as being anticipated by **Haque *et al.*** [Nat. Genet. 20(2), 157-162 (Oct. 1998)]. The examiner stated the following reasons: "Applicants' nucleic acid sequence of SEQ ID NO:9 is identical to accession number AF091242 disclosed in the reference. Applicants' SEQ ID NO:7 is encoded by SEQ IDE NO:9 and the translated sequence is taught by the cited reference."

Applicants have herein attached the Declaration under 37 C.F.R. §1.132, executed July 11, 2001 and originally filed in parent application 09/399,212 on August 8, 2001. (Appended as **Exh. A**). In his Declaration, Dr. Cohn avers that Haque *et al.*, was published less than 12 months before the priority date of the above-captioned application, was co-authored by the named inventors and that the other co-authors did not contribute to the conception of the invention. The Declaration of Dr. Daniel Cohn particularly states that the nucleic acid sequences disclosed in the cited reference, SEQ ID NOS: 1, 2 and 9, are part of the claimed technology in Ser. No. 09/399,212 (the parent application of the above-captioned application, filed on September 17, 1999, subsequently abandoned) and that only the named co-inventors, Daniel Cohn, Muhammad Faiyaz ul Haque, Lily King, and Deborah Krakow, participated in the identification of nucleotide sequences claimed in Ser. No. 09/399,212 and now in the above-captioned 09/898,165. (**Exh. A at ¶ 6**). Additionally, Dr. Daniel Cohn's declaration states that the other co-authors listed on the article, *i.e.*, Rita Cantor, Mike Rusiniak, Richard Swank, Andrea Superti-Furga, Sayedul Haque, Hawssan Abbas, Wasim Ahmad, and Mahmud Ahmad, were not and are not co-inventors of the claimed invention. (**Exh. A at ¶ 8**).

Therefore, the cited reference is eliminated as properly citable art against the claimed invention, under 35 U.S.C. § 102(a). Accordingly, Applicants respectfully request the Examiner to withdraw the rejections on this ground.

(2) The Examiner also rejected Claim 109 under **35 U.S.C. § 102(a)** as being anticipated by **Franzon *et al.*** [Int'l J. of Biochem & Cell Biol. 31:613-626 (May 1999)] under 35 U.S.C. § 102(a) and as being anticipated by **Falco *et al.*** [U.S. Patent No. 6,338,966 (filed July 1, 1999, issued Jan. 15, 2002)] under **35 U.S.C. § 102(e)**. The Examiner asserted that "Franzon *et al.* teach isolation and characterization of nucleotide and the predicted amino acid sequence from human PAPSS2 cDNA." Regarding Falco *et al.*, the Examiner stated, "Falco *et al.* teach an amino acid sequence which is similar to Applicants SEQ ID NO:7 and contains several more than 6 contiguous amino acid fragments (even though the claim does not specify) and therefore reads on the fragment limitation of claim."

In response, Applicants submit a declaration by co-inventor Dr. Daniel Cohn under 37 C.F.R. §1.131, which shows that the claimed invention was reduced to practice before May 22, 1998. (Facsimile appended as **Exh. B**, original will be forwarded to the Examiner when received by Applicants' undersigned attorney). The declaration of Dr. Daniel Cohn particularly states that he executed an Invention Disclosure Form on May 22, 1998, which described the claimed invention. (**Exh. B ¶ 3** and **Exh. B1**). The Invention Disclosure Form predates the effective dates of the references cited by the Examiner, *i.e.*, Franzon *et al.* (May 1999) and Falco *et al.* (provisional application filed on July 14, 1998). Therefore, these cited references are eliminated as properly citable art against the claimed invention, under 35 U.S.C. § 102(a) and 102(e).

Accordingly, Applicants respectfully request the Examiner to withdraw the rejections on this ground.

(3) Claim 109, under **35 U.S.C. § 102(b)**, was also rejected by the Examiner as being anticipated by **Rosenthal *et al.*** [Gene 165:243-48 (1995)]. The Examiner stated:

> **Rosenthal et al. teach a PAPS synthetase sequence which is 72.4% similar to Applicants SEQ ID NO:7 and contains several more than 6 contiguous amino acid fragments (even though the claim does not specify the 6 amino acid fragments to be contiguous) and therefore reads upon the limitations of claim. The cited reference anticipates because it teaches the fragment limitations of the claim.**

Applicants herein have amended Claim 109 by deleting "or an antibody binding fragment thereof at least 6 amino acids long." Applicants believe that the amendment overcomes the rejection because Claim 109 no longer claims any fragments taught by Rosenthal *et al.* Therefore, Applicants respectfully request the Examiner to withdraw the rejection on this ground.

C. Rejection under 35 U.S.C. § 103(a)

The Examiner rejected Claims 110-111 and 114-115 under **35 U.S.C. § 103(a)** in view of **Haque *et al.*** [Nat. Genet. 20(2), 157-162 (Oct. 1998)] or **Franzon *et al.*** [Int'l J. of Biochem & Cell Biol. 31:613-626 (May 1999)] and **Fawell *et al.*** [PNAS USA, 91:664-668 (1994)]. The Examiner stated the following reasons:

Claims 110-111 & 114-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fatyaz ul Haque et al. [Nat. Genet. 20(2), 157-162 (1998, October), IDS] or Franzon et al. (International journal of biochemistry & Cell Biol. 31 (May 1999) 613-626, IDS] and Fawell et al. [PNAS USA, 91:664-668 (1994).

Claims 110-111 & 114-115 are rejected under 35 U.S.C. 102(e) as being anticipated by Fatyaz ul Haque et al. [Nat. Genet. 20(2), 157-162 (1998, October), IDS] or Franzon et al. (International journal of biochemistry & Cell Biol. 31 (May 1999) 613-626, IDS] and Fawell et al. [PNAS USA, 91:664-668 (1994)]. The teachings of Fatyaz ul Haque et al. or Franzon et al. Are described above in item 10 or 11. Fatyaz et al. or Franzon et al. Do not teach making a fusion protein.

Addition or linking of a heterologous polypeptide to make a fusion protein (by forming a hybrid gene) is well know in the art, such as adding a histidine tag, or Tat-meditated delivery of heterologous proteins into cells using TAT protein of human immunodeficiency virus by chemically cross-linking (Fawell et al. See abstract) or by gene fusion (Fawell et al., page 668, column 1, last paragraph) and a skilled artisan would have been motivated to do so in order to achieve a faster and easier method for protein purification(by histidine tag) or by a fusion construct using TAT protein for easier, targeted and efficient delivery of proteins into cells, and therefore an obvious modification. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, *prima facie* obvious.

Applicants assert that Haque *et al.* or Franzon *et al.* are not properly citable against the claimed invention, as discussed above (pages 7-8), in connection with Exhibits A and B. Applicants are confused by the Examiner's citation of **35 U.S.C. § 102(e)**, in the comments quoted above which appear to be mistaken. 35 U.S.C. § 102(e) involves anticipation by an application for patent or a patent granted on an application, which is not at issue here. Clarification is requested.

Further, with respect to the amendments to the Claims 110-111, Claims 110-111 and 114-115 are directed to fusion proteins that comprise "a first PAPSS2 polypeptide segment comprising an amino acid sequence of SEQ ID NO:7; and a second predetermined polypeptide segment." (Claim 110). Amended Claim 111 relates to the fusion protein "wherein the PAPSS2 polypeptide segment is encoded by a nucleic acid segment having a nucleotide sequence of SEQ ID NO:9, or by a degenerate sequence." Fawell *et al.* fails to teach or suggest Tat protein of HIV-1 combined with "PAPSS2 polypeptide segment comprising an amino acid sequence of SEQ ID NO:7" (*e.g.*, Claim 110) or "wherein the PAPSS2 polypeptide segment is encoded by a nucleic acid segment having a nucleotide sequence of SEQ ID NO:9" (*e.g.*, Claim 111). Thus,

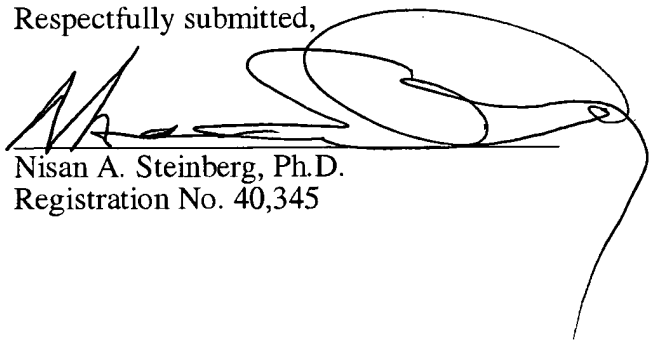
Fawell *et al.*, minus the hindsight provided by the disclosures of Applicants' Specification, fails to make the invention obvious.

Therefore, Applicants respectfully request the Examiner to withdraw the rejection on this ground.

CONCLUSION

In view of the above amendments and remarks, it is submitted that this application is now ready for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,



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INVENTION DISCLOSURE FORM

I. Descriptive Data

1. Descriptive Title of Invention:

   Novel ATP sulfurylase/APS kinase genes from human and mouse.

2. Describe the invention. Use attached sheets, if necessary, and include examples, drawings or other data. If the invention is described in a manuscript that is being prepared for publication, attach a copy.

   The human gene for a previously undescribed protein, an ATP sulfurylase/APS kinase, and its mouse homolog have been isolated. Mutations in the human gene have been shown to be responsible for an inherited dwarfing condition, spondyloepiphyseal dysplasia-Pakistani type. The disease results in short limbs, kyphoscoliosis, and early onset osteoarthritis. Mutations in the mouse gene produce a similar disease, brachymorphic, providing a model in which to test therapeutic strategies.

3. Explain if the invention is a new process, composition of matter, a device or one or more products? A new use for, or an improvement to, an existing product or process?

   The genes are previously undescribed/unknown.

4. Where and when was the invention conceived? Attach annotated copies of any written records that substantiate this conception date. Such records can include notebook entries, letters, reports, etc.

   The genes were identified in the period between March 9, 1998 and the present. The exact date depends on the definition of identified.

5. When did any experimental work relating to the invention first occur? Attach copies of substantiating notebook entries.

   The answer depends on what constitutes the first experimental work. We first began studying the family with the human genetic disease in November of 1996 and began to study the mouse disease in early 1998. However, the identification of the genes was not until March of 1998.

6. State status of experimental work and at what stage of development.

   We have finished characterizing the human gene and have demonstrated that it is the disease gene for the human dwarfing conditi n. Characterization

of the mouse gene is nearly complete and we are still working to identify the genetic defect that produces the mouse disease.

7. Date and place of first test with results (give name and address of witnesses and present location of records).

The first test showing that the mouse and human genes existed was on or about March 9, 1998. The test was an internet search conducted by Daniel H. Cohn and there are neither records nor witnesses. This search, however, can be replicated.

8. How does this invention differ from present technology? Advantages or disadvantages over prior structures or methods?

This is a previously unrecognized gene important for proper synthesis of cartilage. When absent, a human dwarfing condition with early onset degenerative joint disease and osteoarthritis results. Whether defects in this gene could also lead to other inherited diseases or more common arthritic conditions is unknown. If they do, however, distinguishing those that result from defects in this gene from those resulting from alternative mechanisms of disease could become important. Whether manipulation of this or related genes could ameliorate such diseases is also unknown. If it could, however, it could be of potential benefit.

II. Other Pertinent Data

1. Are there laboratory records and data available? Give reference numbers and physical location, but do not enclose.

Laboratory records are available in the laboratory of Daniel H. Cohn, Ph.D., Director of the Collagen Molecular Genetics Laboratory. The lab is located in the Steven Speilberg Building, Room 151.

2. State the nature and extent of any literature search made to date, and attach copies of the closest references found.

The closest related gene is a "sister" gene that encodes a similar enzymatic activity. There are multiple references to that gene, in both human and mouse, as well as to similar genes in many other species.

3. First public disclosure to others: Where? When? And to whom? (specify records relied on).

Disclosure has only been made to collaborators within our research group, including individuals at Cedars-Sinai and one collaborator at Zurich Children's Hospital in Switzerland. The project has been discussed at our laboratory meetings and word of the discovery, without specifics, has gotten out to some extent.

4. Was the work that led to the invention sponsored? If yes, attach copy of contract or agreement if possible, and fill in the appropriate blanks below.

(a.) Title of government agency: **NIH**

(b) Name of industrial company:_____

(c) Name of University sponsor:_____

(d) other sponsor(s):_____

5. Has there been any commercial interest in this invention? Please name companies and specific persons, if available.

No

6. Do you know of other commercial firms who may be interested in your invention?

No

7. What is the prospective commercial value or utility of your idea?

See above - diagnostic testing or therapy.

8. Would your invention be of particular use in foreign countries? (*e.g.*, the invention is a drug for a tropical disease, etc.).

No

9. Name (s) , address (es) and telephone number (s) of person (s) who may be contacted further about the invention.

Daniel H. Cohn x2880

10. Signature(s) of person(s) making this disclosure, including date signed.

Dated: 5/22/98 _____

Printed Name: **Daniel H. Cohn**

Dated: _____ _____

Printed Name: _____

Dated: _____ _____

Printed Name: _____

11. Signature of Department Chairperson (*i.e.* reviewed by):

Dated: 6/4/98 _____

Printed Name: **David L. Rimoin**
Department: **Pediatrics (Medical Genetics)**